

### **REMARKS**

Undersigned counsel thanks Examiner Woitach for extending the courtesy of a telephone interview on January 26, 2005 to discuss the outstanding Office Action and the contents of this Response.

#### **Status of the Claims**

Upon entry of this paper, claims 1-10 will be pending in this application. Solely in the interest of timely prosecution, and without acquiescing to the propriety of the rejections, claims 11-20 have been canceled. Applicants retain, however, the right to pursue the canceled subject matter in a continuation application.

Applicants respectfully request entry of the amendments and remarks made herein into the prosecution history of the present invention. Reconsideration and withdrawal of the rejections set forth in the above-identified Office Action are respectfully requested.

#### **Support for Amendments/ New Claims**

Claims 1, 2 and 7 have been amended; claims 21 and 22 are new. Support for the amendment to claim 1 may be found throughout the specification and, at least, at page 2, paragraph 1. Support for the amendment to claim 2 may be found through out the specification and original claims. Accordingly, Applicants submit that no new matter has been added by this amendment. Reconsideration and allowance of all the claims is respectfully requested.

#### **Elections/Restrictions**

Examiner has withdrawn claims 11-20 from further consideration for being drawn to a non-elected group, the Examiner having found no allowable generic or linking claim. Applicants have cancelled claims 11-20 with this amendment without acquiescing to the position taken by the Examiner.

### **Oath/Declaration**

The Examiner has noted a defective oath or declaration. Specifically, on the signature page of the declaration, the address information for Andreas Ochs has been amended without initials or date, as required by 37 CFR 1.52(c). In the interest of saving the time in obtaining all the signatures on a new declaration, Applicants respectfully request the Examiner to consider that where an Application Data Sheet is submitted with an oath or declaration, the office will rely on the ADS over the oath or declaration per 601.05 (see MPEP page 600-25, second column, first full paragraph). According to 605.03, the Applicant's address only needs to be on the declaration if not supplied on an ADS, which was submitted with the correct inventor address. Because Dr. Ochs' correct address was supplied in the ADS, Applicants respectfully request that the address on the declaration is not material to the issue of inventorship and therefore should not be considered a defect.

### **Specification**

The Examiner has kindly noted that the priority data in the specification appears to be incorrect. In particular, the listing of 08/256,696 should read 08/265,696. Applicants thank the Examiner for noting the inadvertent typographical error and have amended the specification accordingly.

### **Priority**

The Office Action states that the listing of 08/256,696 does not comply with one or more conditions for receiving benefit of an earlier filing date for the reasons of record. As noted above, the listing of 08/256,696 should read 08/265,696, and Applicants have now amended this inadvertent typographical error. Thus, Applicant's respectfully submit that the specification has been properly amended to receive the benefit of the earlier filing date under 35 U.S.C. 120.

### **Claim Objections**

Claim 7 has been objected to for comprising the trademark MILLICELL, which should be capitalized and accompanied by the generic terminology. Applicants have amended claim 7 to capitalize MILLICELL, and Applicants respectfully submit that "membrane support, filters,

sponges, and hollow fiber systems” are generic terms known to one of ordinary skill in the art. Accordingly, Applicants respectfully submit that this objection has been properly overcome.

Claims 2-9 have been objected to under 37 C.F.R. 1.75 as being of improper dependent form for failing to further limit the subject matter of a previous claim. In particular, the Office Action alleges that claim 2 sets forth capabilities of the claimed precursor cell, which appear to be inherent properties of the claimed cell and therefore do not further limit claim 1. Applicants respectfully traverse this objection. It is kindly noted that claim 2 and the claims that depend therefrom do not further limit the claimed cell, but rather further limit the *culture medium*. More specifically, “serum-free” and “extracellular matrix and liver stromal cells” are to be applied to further define the “culture medium” and not the cells of the claimed composition. Thus, Applicants respectfully submit that the claims, as written, properly further limit the base claim.

Nonetheless, solely in the interest of a speedy prosecution, Applicants have amended claim 2 to make explicit what was implied in the original claim language. Thus, the amendment should not be construed to change the scope and/or meaning of claim 2.

Applicants respectfully submit that the present claims have overcome all of the Examiner’s objections, and kindly request allowance of same.

#### **Claim Rejections under 35 U.S.C. § 101**

Claims 1-20 stand rejected under 35 U.S.C. § 101 because the claimed subject matter is directed to non-statutory subject matter. More specifically, the Office Action states that “the claimed cells read on cells that are a human embryo.” Applicants traverse this rejection in maintaining that it is not their intent to claim a human embryo.

One of ordinary skill in the art would appreciate from the disclosure that Applicants’ compositions are not to be equated with a human embryo. Applicants respectfully note the specification adequately describes one method of obtaining the inventive compositions, which method could not yield a human embryo. The specification recites at page 2, first paragraph that “such hepatocyte precursors may be obtained from an excised section of liver. The excised section of liver may then be dissociated by standard procedures into single dissociated cells. Such procedures include enzymatic dissociation and mechanical dissociation. Enzymatic dissociation may be carried out in the presence of protease(s), such as collagenase(s) and/or

nuclease(s), such as DNase. ... The cells are then subjected to an enrichment procedure to eliminate mature liver cells from the cell population.” Of course, one of ordinary skill in the art is able to obtain dissociate cells by other analogous methods.

Nonetheless, without acquiescing in the propriety of the rejection, claim 1 has been amended in accordance with the Examiner’s suggestion to clarify what was implied in the original claim language. The claims, as amended, are directed to composition comprising a cell culture of *isolated* immature animal cells (claim 1); compositions *consisting essentially of* (claims 21); or compositions comprising a population of isolated cells *enriched* (claim 22). Thus, Applicants submit respectfully that the claims, as amended, are directed to patentable subject matter. Applicants request respectfully that the 35 U.S.C. § 101 rejection of the pending claims be withdrawn.

### **Double Patenting**

Claims 1-4 and 8-10 stand rejected under 35 U.S.C. § 101 as claiming the same invention as that of claims 1, 3-7 of prior USP No. 5,789,246; and Claims 1, 6, and 7 stand rejected under 35 U.S.C. § 101 as claiming the same invention as that of claims 1-3 of prior USP No. 6,146,889. The Office Action alleges that the pending claims are exactly the same or duplicates of the claims in the respective prior patents. Applicants respectfully traverse this rejection.

The pending claims recite, in relevant part, “a population of hepatocyte precursor cells capable of differentiating into *biliary cells*.” (Emphasis added.) In marked contrast, the prior art claims recite, in relevant part “a population of hepatocyte precursor cells capable of differentiating into *hepatocytes*...” (Emphasis added.) The term, “biliary cells” was introduced by way of Preliminary Amendment, filed August 22, 2003, support for which may be found, at least, at page 16, lines 16-18.

One of ordinary skill in the art would appreciate that biliary cells that form the bile duct are distinct from hepatocytes that form the liver. For at least this reason, Applicants respectfully submit that the pending claims are not coextensive in scope with the patented claims, and thus do not claim the same invention as defined for § 101.

### **Obviousness-type Double Patenting**

Claims 1-10 stand rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims in USP Nos. 6,146,889; 5,789,246; and/or 5,576,207. Although the conflicting claims are not identical, they have been deemed patentably indistinct from each other for reasons of record.

Without acquiescing to the propriety of the rejection, Applicants are filing herewith Terminal Disclaimers for each of the patents mentioned above. Applicants note respectfully that "[T]he filing of a terminal disclaimer to obviate a rejection based on nonstatutory double patenting is not an admission of the propriety of the rejection." M.P.E.P. §804.02(II).

In view of the Terminal Disclaimers concurrently submitted herewith over each of U.S. Patent Nos. 6,146,889; 5,789,246; and 5,576,207, Applicants respectfully submit that the obviousness-type double patenting rejections have been overcome and withdrawal thereof is respectfully requested.

### **Claim Rejections under 35 U.S.C. § 112, second paragraph**

Claims 2-9 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter the Applicants regards as the invention. More specifically, the Office Action alleges "that claims 2-9 are confusing and unclear because what is being claimed appears to be an inherent property of the cell claimed in claim 1, and the metes and bounds of the claims set forth by these dependent claims are indefinite because it is unclear how they further limit claim 1 or what cells from claim 1 specifically have the claimed capabilities." Applicants respectfully traverse this rejection.

For the reasons expounded under "claim objections," Applicants point out that the dependent claims do not further limit the claimed cell, but rather further limit the culture medium. Thus, Applicants respectfully submit that the claims, as written, properly further limit the base claim. Nonetheless, without acquiescing in the propriety of the rejection, Applicants have amended claim 2 to make explicit what was implied in the original claim language.

Applicants submit respectfully that the claims, as amended, are not unclear. Applicants request respectfully that the 35 U.S.C. § 112, second paragraph, rejection of the pending claims be withdrawn.

### Claim Rejections under 35 U.S.C. § 102

Claims 1-10 stand rejected for being anticipated by USP No. 5,030,105 to Kuri-Harcuch *et al.* (hereinafter, “Kuri-Harcuch”). Specifically, the Examiner states that Kuri-Harcuch teaches and isolated liver and provides guidance such as media and appropriate substrates for the in vitro culturing of cells. Moreover, it is alleged that claim 1 “encompasses any composition [e.g., a liver] of immature animal cells that contains a population of cells that are capable of differentiating into hepatocytes.” Applicants respectfully traverse this rejection.

First, Applicants kindly note that that pending claims read, in part, “cells capable of differentiating into *biliary cells*,” not hepatocytes as written in the Office Action. Second, Applicants submit respectfully that amended claim 1 as well as the newly added claims make clear that the claimed invention is not directed to whole liver (see argument presented above) and therefore not anticipated by the prior art.

Finally, Kuri-Harcuch teaches the culturing of *mature* hepatocytes (not hepatocytes *precursors*) in the presence of fibroblasts and hormones such as hydrocortisone and insulin, for example. Such culturing provides for a long-term survival of the hepatocytes so that the hepatocytes may be available for use in methods for the assessment of the effects of toxicological, chemical, biological, and pharmacological agents upon the cells. Thus, the difference in the claimed composition and the prior art is reflected in the different objects of Kuri-Harcuch and Applicants’ invention. Applicants teach the culturing of immature cells (hepatocytes *precursors*) in the presence of an extracellular matrix and liver stromal cells in order to expand such cells without necessarily differentiating the expanded cells. In contrast, Kuri-Harcuch teaches the culturing of mature hepatocytes to enable the long-term survival of such hepatocytes.

Accordingly, Applicants submit respectfully that the claims of the present invention, as amended, are not anticipated by the prior art, which does not teach or suggest each and every element of the present claims. Hence, the rejection under 35 U.S.C. § 102(b) has been overcome. Applicant requests respectfully that the rejection under 35 U.S.C. § 102(b) be withdrawn.

Claims 1-10 also stand rejected for being anticipated by Tsai *et al.* (Biol. Abstr. 22434-IDS reference) (hereinafter, "Tsai"), under 35 U.S.C. § 102(b). In particular, the Office Action states that the breadth of the claims read on, for example, an isolated (fetal) liver as taught by the prior art. Applicants traverse respectfully.

Applicants submit respectfully that amended claim 1 as well as the newly added claims are not anticipated by the prior art. The claimed invention is directed to hepatocyte precursor cells. As used in the present invention, "hepatocyte precursor cells" are immature liver cells which are capable of differentiating into adult liver cells such as hepatocytes, bile duct cells, liver endothelial cells, lipid-containing liver cells known as Ito cells, and the like (see page 16, lines 14-19). The term "hepatocyte precursor cells" does not include "hemopoietic progenitors."

The Examiner correctly notes that Tsai teaches conditions for culturing cells and indicates that ST-1 cells provide growth factors to the media when cultured *in vitro*. However, the "cells" referred in Tsai are "hemopoietic progenitors" and the growth factors are *hemopoietic* growth factors. In other words, Tsai does not teach the development of hepatocytes or bile duct cells. Applicants' invention, on the other hand, do concern *hepatocyte* precursor cells capable of differentiating into biliary cells.

Applicants maintain that Tsai does not teach or disclose compositions of the claimed invention. Accordingly, Applicants submit respectfully that the claims of the present invention, as pending, are not anticipated by the prior art, which does not teach or suggest each and every element of the present claims. The rejection under 35 U.S.C. § 102(b) having been overcome. Applicant requests respectfully that the rejection under 35 U.S.C. § 102(b) be withdrawn.

**CONCLUSION**

Applicants submit that the application is in condition for allowance. Favorable reconsideration, withdrawal of the rejections set forth in the above-noted Office Action, and an early Notice of Allowance are requested.

Applicants' undersigned attorney may be reached in our Washington, D.C. office by telephone at (202) 625-3500. All correspondence should be directed to our address given below.

**AUTHORIZATION**

Applicants believe there is no fee due in connection with this filing. However, to the extent required, the Commissioner is hereby authorized to charge any fees due in connection with this filing to Deposit Account 50-1710 or credit any overpayment to same.

Respectfully submitted,



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